REMARKS

Claims 2, 3, 5, 7, and 8 are pending in the application. New claims 15 and 16 have been added by this amendment. Therefore, claims 2, 3, 5, 7, 8, 15, and 16 are at issue.

In this amendment, new claims 15 and 16 have been added to recite that a pharmaceutical agent of formula (I) treats neuropathies separately from a peripheral diabetic polyneuropathy (claim 15) and that the treatment of a peripheral diabetic polyneuropathy consists of application of a compound of formula (I). Support for these new claims can be found in pending claim 1 and in Examples 1 and 2 of the specification at pages 4 and 5.

Claims 2, 3, 5, 7, and 8 stand rejected under 35 U.S.C. §112 as being indefinite because a nitrogen atom missing from the structure for compounds I, Ia, and III. Applicants apologize for this typographical error noted by the examiner, and has amended the claims to recite the correct structure. In view of the amendments to the claims, it is submitted that this rejection has been overcome and should be withdrawn.

Claims 2, 3, 5, 7, and 8 stand rejected under 35 U.S.C. §103 as being obvious over DuBois U.S. Patent No. 6,399,601 ('601) in view of U.S. Patent No. 5,972,342 ('342) and further in view of U.S. Patent No. 5,753,225 ('225). The rejection is based on a contention that the '601 patent teaches a composition containing sildenafil for treating diabetes and diabetic complications. For the reasons set forth below, it is

submitted that this rejection is in error and should be withdrawn.

First, the examiner mischaracterizes the '601 patent. The '601 patent is directed to compounds of Formula I that (a) *differ substantially* from sildenafil and (b) are useful in the treatment of diabetes *and* in the treatment of diabetic complications, including neuropathy ('601 patent, column 23, line 63 through column 24, line 2). More particularly, the '601 patent states:

> "Diabetes can be treated by administering to a patient having diabetes (Type I or Type II), insulin resistance, impaired glucose tolerance, or any of the diabetic complications such as neuropathy, nephropathy, retinopathy or cataracts, *a therapeutically effective amount of a compound of the present invention*. It is also contemplated *that diabetes be treated* by administering a compound of the present invention or an other [sic] glycogen phosphorylase inhibitors that are useful in combination with other agents useful to treat diabetes and/or obesity include those of Formula I. Additional preferred glycogen phosphorylase inhibitors are disclosed in PCT publications WO 96/39384 and WO 96/39385." (column 24, lines 3-17, emphasis added).

The '601 patent goes on to disclose that a litany of other drugs having several different modes of action can be used *in conjunction with* the compounds of Formula I to *treat* diabetes (column 24, line 18 through column 28, line 16). The list at column 24, lines 18-67 alone contains no less than *thirty* classes of

compounds, and a multitude of individual compounds, that act by inhibiting vastly different enzymes or by other unrelated biological processes. Importantly, this litany of other drugs is taught merely as "representative agents that can be used to *treat diabetes*" ('601 patent, column 24, line 18, emphasis added). The long list of compounds disclosed in the '601 patent as agents to *treat diabetes* includes cAMP- and cGMP-type inhibitors, such as sildenafil (column 24, lines 37-38).

The compounds of Formula I of the '601 patent have a favorable effect upon blood sugar, which leads to a decrease of diabetes-*specific* complications, including neuropathies associated with diabetes. The '601 compounds, however, would have no effect on neuropathies *not* associated with diabetes. In contrast, the present claims provide a treatment for the neuropathies recited in claim 1, including *non*diabetes-related neuropathies. The compounds of Formula I of the '601 patent also cannot be compared to the presently claimed compounds because the presently claimed compounds do not work via a reduction of blood sugar, but most likely *via* an improved blood supply to the peripheral nerve tissue.

The '601 patent clearly states that compounds of Formula I (which differ from sildenafil in structure *and* mode of action) treat diabetes *and* diabetic complications. The '601 patent then goes on to state that other agents can be used with a compound of Formula I to treat *diabetes*. These other agents are not taught

as being capable of treating either diabetic complications or neuropathies *un*associated with diabetes.

Furthermore, the '601 patent *requires* that compound of Formula I be present in the composition to treat diabetic complications. Applicants have found that the neuropathies recited in claim 5 can be treated by the compounds recited in claim 5 *alone*, without requiring the presence of a compound of Formula I. See Examples 1 and 2 of the specification. This is a new and unexpected finding in view of the '601 patent that *requires* the presence of a compound of Formula I.

The examiner notes that the present claims do not *exclude* the use of a compound of Formula I. The exclusion of a compound of Formula I is not necessary to patentably distinguish the present claims over the '601 patent disclosure. The '601 patent fails to teach or suggest that sildenafil can be used to treat diabetic neuropathies *or any* other neuropathy. The '601 patent merely states that the compounds of Formula I treat diabetes *and* complications, such as diabetic neuropathies, *and* that sildenafil can be used to treat diabetes. The fact that an individual suffering from diabetes *may elect* to undergo a combination treatment using a compound of Formula I of the '601 and a second drug disclosed in the '601 patent, including sildenafil, to enhance the treatment of diabetes does not negate the teaching the '601 patent, i.e., that the second drug treats diabetes.

The present claims are directed to compounds that treat neuropathies both in individuals suffering from diabetes and in individuals who do not suffer from

diabetes. Any potential combination treatment suggested by the examiner is not a basis to conclude that it would have been obvious to use a presently claimed compound to treat *neuropathies* associated with the diabetes, or *any* other neuropathy.

The examiner also should note that the neuropathies recited in new claim 15 are *not* related to diabetes. In addition, new claim 16 recites that a claimed compound is the sole agent to treat a diabetic-related neuropathy. The '601 patent fails to teach or suggest that sildenafil can be used alone to treat diabetic neuropathies. Throughout the '601 patent, it is taught that a compound of Formula I is necessary for the treatment of diabetes *and* complications of diabetes. The '601 patent also states that a compound of Formula I can be used with a second agent useful in the treatment of diabetes. However, sildenafil is *not* taught in the '601 patent as a drug to treat complications of diabetes, but to actually treat the *diabetes*.

In contrast to the '601 patent, the present method utilizes sildenafil to treat neuropathies, *not* to treat diabetes. In Examples 1 and 2 of the specification, the patients were administered sildenafil to achieve an improvement of symptomatic pain and the symptoms and complications of diabetes, but *not* the disease itself.

The secondary and tertiary references do not overcome the deficiencies of the '601 patent. The '342 patent is directed to grain-derived mixtures and use of the same as medicaments. The '342 patent fails to add to the '601 patent, and fails to suggest that silden-

afil can treat diabetic or nondiabetic neuropathies. The portion of the '342 patent relied upon by the examiner merely is a list of diabetic complications and a list of other disease conditions purportedly treated by the disclosed grain-derived mixtures. The mixtures of the '342 patent are not related to sildenafil in general, or to phosphodiesterase inhibitors in general, thus there is no motivation to combine the teachings of the '601 patent and the '342 patent and arrive at the presently claimed invention.

The tertiary '225 patent is directed to antibodies that mimic neurotrophins. The '225 patent is relied upon by the examiner for teaching the etiologies of a peripheral neuropathy. But the '225 patent, like the '342 patent, absolutely fails to teach or suggest that a phosphodiesterase inhibitor can be used to treat neuropathies. Applicants fail to find any disclosure in the '225 patent, or the '342 patent, that adds to the teachings of the '601 patent, such that a person skilled in the art would have been motivated to treat a neuropathy (as opposed to diabetes) using a compound presently claimed in claim 5 alone (as compared to using a claimed compounds in combination with a compound of Formula I of the '601 patent). Although the '342 and '225 patents teach neuropathies and the etiology of neuropathies, these references in combination with the '601 reference fail to teach *treatment* of a peripheral diabetic polyneuropathy, a toxic neuropathy, gastroparesis, a degenerative neuropathy, or a metabolic neuropathy with a compound recited in the present claim 5.

For all the reasons set forth above, it is submitted that a person skilled in the art, after considering the combined teachings of the '601, '342, and '225 patents would have had no incentive to consider using a compound presently claimed in claim 5 to treat a recited *neuropathy*. Accordingly, the rejection of claims 2, 3, 5, 7, and 8 as being obvious over the cited '601, '342, and '225 patent should be withdrawn. It also is submitted that new claims 15 and 16 are patentable over the combination of cited references for all the reasons set forth above.

In summary, it is submitted that all pending claims are in a form and scope for allowance. An early and favorable action on the merits is respectfully requested.

Should the examiner wish to discuss the foregoing, or any matter of form in an effort to advance this application toward allowance, the examiner is urged to telephone the undersigned at the indicated number.

Respectfully submitted,

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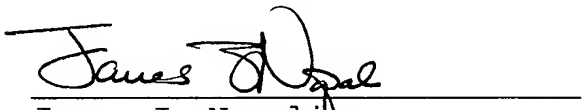
By 

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January 10, 2006